

# The Role of Transbronchial Fine Needle Aspiration in an Integrated Care Pathway for the Assessment of Patients with Suspected Lung Cancer

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Transbronchial fine needle aspiration (TBNA) is a simple technique for sampling mediastinal lymph nodes and may provide additional information in patients with suspected lung cancer. However, the technique is still under-utilized, and the objective of this study was to evaluate the value of TBNA as part of an integrated pathway for the assessment of patients with suspected lung cancer. All patients referred to the lung cancer services of our institutions were prospectively evaluated. TBNA was performed in all patients with evidence of mediastinal lymphadenopathy. TBNA of one or more lymph node sites were performed in 129 of these patients. TBNA was the sole diagnostic modality in 23% of patients and provided positive staging information for 49% of patients, with adequate sampling in 71% of patients. Among patients with mediastinal adenopathy, the number of patients who required a TBNA performed to diagnose one patient with malignancy in patients suspected with lung cancer (number needed to diagnose) was 1.47 (95% confidence interval, 1.47–1.76). No complications were observed in patients who underwent TBNA. TBNA improves the diagnostic yield and staging of patients with lung cancer. Moreover, it is a simple, low-cost, and safe test, which should be incorporated into the diagnostic pathway of patients with suspected lung cancer.

**Key Words:** Lung cancer, Bronchoscopy, Transbronchial fine needle aspiration, Integrated care pathway.

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**L**ung cancer is the third most common cause of death in the Western World among both men and women. In the United Kingdom, there are more than 35,000 new cases of lung cancer each year, and the overall prognosis remains poor. Treatment is dependent on accurate histological or cytological diagnosis and accurate staging. Lung cancer occurs more frequently in the elderly, and patients also fre-

quently have significant disease morbidity; therefore, it is important to obtain accurate staging by the least invasive investigation. Transbronchial needle aspiration (TBNA) via the rigid bronchoscope was first described in 1949<sup>1</sup> and was adapted for the flexible bronchoscope by Wang.<sup>2</sup> However, this technique is still under-utilized despite a number of reports in the literature. A North American bronchoscopy survey suggested that only 11.8% of respondents used TBNA routinely for cases in which malignant disease was suspected.<sup>3</sup> A subsequent survey among pulmonary fellows demonstrated that the proportion that routinely uses TBNA is still approximately 10%.<sup>4</sup> We prospectively evaluated patients with suspected lung cancer who underwent flexible bronchoscopy and evaluated the added value of TBNA in routine clinical practice.

## METHODS

All patients referred to our rapid access clinics (Chelsea & Westminster Hospital or Royal Brompton Hospital) with suspected lung cancer were prospectively evaluated. All the assessments were made as part of the routine clinical evaluation of patients with lung cancer from December 1999 through June 2003. TBNA was performed using a 21-gauge needle (NAC-1; Olympus, Tokyo, Japan) in all patients who had mediastinal lymph nodes larger than 10 mm in short axis on computed tomograms (CT) of the thorax. The procedures were planned according to the axial CTs of the thorax, and the nodes that could be sampled were determined. The accessible sites were right paratracheal nodes, left paratracheal nodes, anterior carinal nodes, posterior carinal nodes, subcarinal nodes, right main bronchial, left main bronchial, right upper hilar, right lower hilar, sub-subcarinal nodes, and left lower hilar. TBNA was performed before inspection or sampling of the tracheo-bronchial tree. This was to minimize the risk of false-positive contamination by malignant cells from the distal airway. The needle with the protective sheath was introduced through the bronchoscope channel so that approximately 5 mm of the distal tip was visible. This was apposed to the airway wall at the desired site and the needle was inserted perpendicular to the airway wall by a jabbing technique until the full 13-mm length had penetrated the airway wall. With the jabbing technique, the bronchoscope position is fixed, and the needle is pushed perpendicularly through the

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intercartilagenous space by a firm and quick push of the catheter. The needle was then moved in and out while the assistant applied constant suction with a 20-ml syringe. Four passes of the needle were made at each lymph node location. The aspirated material was spread onto cytology slides, and smears were prepared for subsequent off-site cytological examination. Any small pieces of tissue obtained were placed in formalin for histological analysis.

Accuracy of TBNA was based on the presence of lymphocytes within the specimen, confirming that the specimen was obtained from lymph node aspiration. Patelli et al.<sup>5</sup> suggested that the sample should have at least 30% of lymphocytes to be considered appropriate, but our view was that this is an arbitrary number and that the key message is that a negative result may be a false negative and should be further investigated. A positive diagnosis for cancer was based on the presence of carcinoma cells, typically mixed in with lymphocytes. Samples without malignant cells but with lymphocytes cannot confidently exclude metastatic disease. Therefore, patients with a negative diagnosis underwent further investigation such as positron emission tomography (PET) and mediastinoscopy. In eight cases, no further investigations were performed on the basis of a confident diagnosis of non-malignant disease. These patients had at least 18 months' follow-up before they were considered true negatives. Any patients with a final diagnosis of malignant disease, but a negative TBNA who did not have a mediastinoscopy (patient refusal or unfit for surgery) were regarded as false negatives for the purpose of the study.

### Statistical Analysis

All patient data for the cohort of 827 patients were prospectively collected. Descriptive analysis of continuous variables is presented as means and standard deviations, whereas nominal variables are presented as medians and interquartile ranges. The reliability of the diagnostic test was estimated by calculating the sensitivity, specificity, and positive and negative predictive values. The number needed to diagnose (NND) was calculated the same way the number needed to treat was estimated.<sup>6</sup> The NND is the reciprocal of the fraction of positive tests in the group with the disease minus the fraction of positive tests in the group without the disease. Thus  $NND = 1/(\text{Sensitivity} - [1 - \text{Specificity}])$ .

### RESULTS

During the study period (December 1999 to June 2003), 827 patients were referred to our lung cancer service with suspected malignancy. Of the 827 patients, 482 (58%) were male, and the median age was 67.5 years. A final diagnosis of malignancy was made in 561 of these patients and was confirmed pathologically in 502 (89%) patients (363 non-small cell lung cancer, 54 small cell lung cancer, 12 other primary lung cancers, 15 mesotheliomas, and 58 lung metastases from other primary tumors). A bronchoscopy was performed in 433 patients, and 129 of these patients (30%) also underwent a TBNA at the same time as their diagnostic bronchoscopy. The initial CT scan for 128 patients demonstrated an alternative means of obtaining a diagnosis and staging information such as pleural aspiration, supraclavicular

lymph node biopsy or liver biopsy. For the remaining 266 patients, the initial CT scan was sufficient to exclude lung cancer.

TBNA was the sole mode of diagnosis for 30 patients (23%) and provided staging information in 63 patients (49%). Of these patients, 47 had N2 disease, four had N3 disease, and 12 had limited-stage small cell lung cancer. All patients with lymph nodes larger than 10 mm in short axis underwent TBNA of the enlarged lymph nodes at bronchoscopy, and in this group, the number of patients who required a TBNA performed to diagnose one patient with malignancy (NND) was 1.47 (95% confidence interval [CI] 1.47–1.76) (Table 1). The diagnostic accuracy of TBNA was 78% (95% CI 70%–85%) with a sensitivity of 68% (95% CI 59%–78%), and specificity of 100%. There were 29 false-negative results, and three of these patients had a final diagnosis of lymphoma. Sixteen patients underwent a mediastinoscopy, but 13 patients were either deemed unsuitable for surgical intervention or refused surgery.

A total of 197 different lymph node groups were sampled (Table 2). A single lymph node group was sampled in 52% of patients, two separate lymph node groups were sampled in 40%, and three or more different lymph node groups were sampled in 8%. Overall, 71% of lymph nodes were adequately sampled, and tumor cells were present in 44% of patients (Table 2). Right paratracheal lymph nodes were most frequently sampled. Adequate sampling, indicated by the presence of lymphocytes or tumor cells, was achieved in 72% of the right paratracheal lymph nodes sampled, and malignant cells were detected in 43%. Subcarinal lymph nodes were also frequently enlarged, and tumor cells were found in 50% of nodes sampled. The other more frequently sampled lymph node station was the anterior carinal node, with a 35% positive yield for cancer.

Lymph node size was a key determinant of success: sensitivity was 63% for lymph nodes smaller than 20 mm and 71% for lymph nodes equal to or larger than 20 mm (Table 3). For lymph nodes larger than 20 mm, the NND was only 1.2 (95% CI, 1.2–3.0).

Histological specimens were obtained from 38 lymph node sites. In this group, the accuracy was higher, 87%

**TABLE 1.** Characteristics of transbronchial fine needle aspiration of mediastinal lymph nodes

	Disease present	Disease absent
TBNA positive	63	0
TBNA negative	29	37
		<b>95% confidence interval</b>
Sensitivity	68%	59%–78%
Specificity	100%	100%
Accuracy	78%	70%–85%
Positive predictive value	100%	95%–100%
Negative predictive value	56%	44%–67%
Number needed to diagnose	1.46	1.46–1.76

**TABLE 2.** Transbronchial fine needle aspiration diagnostic yield according to lymph nodes sampled

Site	Lymph nodes sampled	Mean size of node(mm)	Adequate sampling (tumor/lymphocytes)	Tumor cells identified	Prevalence	Sensitivity
Right paratracheal	58	17	72%	43%	66%	68%
Left paratracheal	17	17	47%	41%	83%	60%
Subcarinal	57	18	73%	50%	71%	72%
Anterior carinal	32	17	79%	35%	71%	45%
Posterior carinal	9	18	87%	67%	78%	86%
Right main bronchial	8	18	33%	25%	62%	40%
Left main bronchial	2	17	100%	50%	-	-
Right hilar	9	14	75%	44%	50%	75%
Left hilar	5	11	100%	20%	80%	25%
Total	197	17	71%	44%	70%	59%

**TABLE 3.** Yield according to lymph node size

	≤19 mm	≥20 mm
Sensitivity (95% CI)	63% (49%–63%)	71% (60%–71%)
Specificity (95% CI)	100%	100%
NND	1.6 (1.6–3.4)	1.2 (1.2–3.0)

CI, confidence interval; NND, number needed to diagnose.

(prevalence 55%, sensitivity 76%). However, the key advantage in these cases was that the pathologist had greater confidence with the diagnosis, and immunostaining could be used to further characterize the tumor.

There were no adverse events observed in any patient who underwent TBNA. Specifically, none of the patients developed a pneumothorax, pneumomediastinum, or hemorrhage (more than 50 ml). Minor bleeding was the only adverse event attributable to TBNA.

## DISCUSSION

TBNA significantly improves the diagnostic yield and staging information for patients with suspected lung malignancy. Moreover, in this study, we further demonstrated its safety, cost-effectiveness, and ease of incorporation into an integrated care pathway for the diagnosis and staging of lung cancer. Furthermore, the complication rate of TBNA is significantly lower than that observed for transbronchial lung biopsies. In this series of patients, there were no significant complications. The incidence of pneumothorax, pneumomediastinum, and hemorrhage derived from studies in the literature is low and ranges from 0.05% to 0.2%.<sup>1,5,7–17</sup> The sensitivity and accuracy from our unselected series are broadly comparable to previously published series.<sup>5,7–17</sup> In our analysis, patients with a negative or inconclusive TBNA who did not have further surgical assessment were considered to have false-negative results; hence, the results presented may be more conservative than the actual findings. Furthermore, in this unselected series of patients, TBNA was performed for all individuals with mediastinal nodes measuring 10 mm or larger, and the prevalence of disease was approx-

imately 60%. In contrast, the only other comparable series reported a prevalence rate of only 34%.<sup>9</sup>

The advantages of TBNA are that it can be established in any bronchoscopy unit with minimal cost and that it can be performed at the same time as the initial diagnostic bronchoscopy. Consequently, it can be performed in any individual who is fit for bronchoscopy and can be incorporated into the diagnostic pathway without any delays in patient assessment. It also minimizes the number of investigations that patients require for both diagnosis and staging. In this cohort, incorporating TBNA into the diagnostic bronchoscopy identified 49% of patients who had cancer cells in their mediastinal lymph nodes aspirates and were therefore spared further, more hazardous surgical staging investigations. Hence, only patients with negative sampling required either additional investigations to confirm malignancy or further clinical follow-up to confirm suspected benign disease.

PET is a useful tool in the staging of patients with lung cancer. It has a sensitivity of 84% and specificity of 89%, and with combined CT-PET, the sensitivity improves to 93% and specificity to 95%.<sup>18</sup> However, with respect to the mediastinum, there is still a false-positive rate of 10% to 15%.<sup>19</sup> Hence, it is strongly advocated that positive results on PET scanning should be confirmed by cytopathology.<sup>20</sup>

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is an alternative technique that allows staging of the mediastinum.<sup>21–24</sup> The yield may be higher than TBNA, but it is only able to sample nodes that are adjacent to the esophagus and unable to examine right paratracheal, anterior carinal, and right main bronchial nodes, as they are not adjacent to the esophagus, and the ultrasound is unable to penetrate the air within the trachea. In our unselected cohort, the latter lymph nodes accounted for more than 50% of enlarged lymph nodes that were involved by metastatic disease. Hilar lymph nodes are also inaccessible by EUS-FNA. The technique also requires a significant capital investment that includes an ultrasound imaging system (113,000 euros), a special linear array echo-endoscope (80,000 euros), a radial echo-endoscope (80,000 euros), specialist cleaning equipment, and considerable staff training. In comparison, TBNA requires no capital costs other than the special needles (ap-



proximately 44 euros per procedure), and the bronchoscopy staff require minimal additional training. With EUS-FNA, the procedure must also be arranged separately from the initial diagnostic bronchoscopy, and the expertise is currently only available in some centers.

Endobronchial ultrasound guided TBNA (EBUS-TBNA) has a higher yield when all lymph node stations are considered (58% with conventional TBNA compared with 84% with ultrasound guidance), but there was no statistical advantage when subcarinal nodes are considered alone (74% versus 84%).<sup>25</sup> Newer integrated bronchoscopes with a linear array probe built into the bronchoscope allow EBUS-TBNA of mediastinal lymph nodes under direct ultrasound control, but this has the same logistical and financial limitations as EUS-FNA.<sup>26,27</sup> The sensitivity of EBUS-TBNA ranges from 85% to 96%.<sup>26–28</sup> Although image-guided TBNA is superior to conventional TBNA, it is only available in a limited number of centers worldwide.

Mediastinoscopy remains the gold standard for staging the mediastinum but requires general anesthesia and still carries the risk of morbidity.<sup>29</sup> The complication rate is approximately 2.5% and includes hemorrhage, pneumothorax, mediastinitis, esophageal perforation, trauma to the azygos vein, and recurrent laryngeal nerve. It is therefore usually reserved for patients who are considered potential surgical candidates. Furthermore, TBNA is able to access more deeply placed nodes, such as the posterior carinal nodes and hilar nodes. We therefore suggest that all patients undergoing bronchoscopy for suspected lung cancer be considered for TBNA if there is CT or PET evidence of mediastinal disease. A combination of EUS-FNA and EBUS-TBNA should be used where the services are available, but, at the very least, blind TBNA should be considered for patients with mediastinal adenopathy.

In conclusion, TBNA is a safe technique that can be easily performed at the time of a diagnostic bronchoscopy. The procedure is low cost, not least as it obviates the need for mediastinoscopy in 50% of cases, and significantly improves the diagnostic yield and staging information for patients with suspected malignancy.

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